Gabitril—Cont.

apathy, choreoathetosis, circumoral paresthesia, CNS neoplasm, coma, delusions, dry mouth, dystonia, encephalopathy, hemiplegia, leg cramps, libido increased, libido decreased, movement disorder, neuritis, neurosis, paralysis, peripheral neuritis, psychosis, reflexes increased, and urinary retention.

Respiratory System: *Frequent:* Bronchitis, dyspnea, epistaxis, and pneumonia. *Infrequent:* Apnea, asthma, hemoptysis, hiccups, hyperventilation, laryngitis, respiratory disorder, and voice alteration.

Skin and Appendages: *Frequent:* Alopecia, dry skin, and sweating. *Infrequent:* Contact dermatitis, eczema, exfoliative dermatitis, furunculosis, herpes simplex, herpes zoster, hirsutism, maculopapular rash, psoriasis, skin benign neoplasm, skin carcinoma, skin discolorations, skin nodules, skin ulcer, subcutaneous nodule, urticaria, and vesiculobullous rash.

Special Senses: *Frequent:* Abnormal vision, ear pain, otitis media, and tinnitus. *Infrequent:* Blepharitis, blindness, deafness, eye pain, hyperacusis, keratoconjunctivitis, otitis externa, parosmia, photophobia, taste loss, taste perversion, and visual field defect.

Urogenital System: *Frequent:* Dysmenorrhea, dysuria, metrorrhagia, urinary incontinence, and vaginitis. *Infrequent:* Abortion, amenorrhea, breast enlargement, breast pain, cystitis, fibrocystic breast, hematuria, impotence, kidney failure, menorrhagia, nocturia, papanicolaou smear suspicious, polyuria, pyelonephritis, salpingitis, urethritis, urinary urgency, and vaginal hemorrhage.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of GABITRIL have not been evaluated in human studies.

OVERDOSAGE

Human Overdose Experience: Human experience of acute overdose with GABITRIL is limited. Eleven patients in clinical trials took single doses of GABITRIL up to 800 mg. All patients fully recovered, usually within one day. The most common symptoms reported after overdose included somnolence, impaired consciousness, agitation, confusion, speech difficulty, hostility, depression, weakness, and myoclonus. One patient who ingested a single dose of 400 mg experienced generalized tonic-clonic status epilepticus, which responded to intravenous phenobarbital.

Eleven individuals (including five children <7 years old) not in tiagabine clinical trials accidentally ingested tiagabine in single doses up to 20 mg. These individuals were asymptomatic in six cases. Symptoms exhibited in at least one of the other five individuals included ataxia, confusion, somnolence, impaired consciousness, impaired speech, agitation, lethargy, drowsiness, and myoclonus. One individual experienced a tonic-clonic seizure but was taking other agents which may be associated with seizures. All individuals recovered, usually within one day.

Management of Overdose: There is no specific antidote for overdose with GABITRIL. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of clinical status of the patient. Since tiagabine is mostly metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial. A Certified Poison Control Center should be consulted for up to date information on the management of overdose with GABITRIL.

DOSAGE AND ADMINISTRATION

GABITRIL (tiagabine HCl) is recommended as adjunctive therapy in patients 12 years and older. GABITRIL is given orally and should be taken with food.

Adequate and controlled clinical studies with GABITRIL were conducted in patients taking enzyme-inducing AEDs (e.g., phenytoin, carbamazepine, and barbiturates). Patients taking only non-enzyme-inducing AEDs (e.g., valproate, gabapentin, and lamotrigine) may require lower doses or a slower titration of GABITRIL for clinical response.

Adults and Adolescents 12 Years or Older: In adolescents 12 to 18 years old, GABITRIL should be initiated at 4 mg once daily. Modification of concomitant antiepilepsy drugs is not necessary, unless clinically indicated. The total daily dose of GABITRIL may be increased by 4 mg at the beginning of Week 2. Thereafter, the total daily dose may be increased by 4 to 8 mg at weekly intervals until clinical response is achieved or up to 32 mg/day. The total daily dose should be given in divided doses two to four times daily. Doses above 32 mg/day have been tolerated in a small number of adolescent patients for a relatively short duration.

In adults, GABITRIL should be initiated at 4 mg once daily. Modification of concomitant antiepilepsy drugs is not necessary, unless clinically indicated. The total daily dose of GABITRIL may be increased by 4 to 8 mg at weekly intervals until clinical response is achieved or, up to 56 mg/day. The total daily dose should be given in divided doses two to four times daily. Doses above 56 mg/day have not been systematically evaluated in adequate well-controlled trials.

Experience is limited in patients taking total daily doses above 32 mg/day using twice daily dosing. A typical dosing titration regimen for patients taking enzyme-inducing AEDs is provided in Table 6.

[See table 6 on previous page]

HOW SUPPLIED

GABITRIL Filmtab tablets are available in five dosage strengths.

2 mg orange-peach, round tablets, debossed with ⊟ on one side and the Abbo-Code FJ on the opposite side, are available in bottles of 100 (NDC 0074-3963-13).

4 mg yellow, round tablets, debossed with ⊟ on one side and the Abbo-Code FK on the opposite side, are available in bottles of 100 (NDC 0074-3904-13).

12 mg green, ovaloid tablets, debossed with ⊟ on one side and the Abbo-Code FL on the opposite side, are available in bottles of 100 (NDC 0074-3910-13).

16 mg blue, ovaloid tablets, debossed with ⊟ on one side and the Abbo-Code FM on the opposite side, are available in bottles of 100 (NDC 0074-3960-13).

20 mg pink, ovaloid tablets, debossed with ⊟ on one side and the Abbo-Code FN on the opposite side, are available in bottles of 100 (NDC 0074-3982-13).

Recommended Storage: Store tablets at controlled room temperature, between 20–25°C (68–77°F). See USP. Protect from light and moisture.

ANIMAL TOXICOLOGY

In repeat dose toxicology studies, dogs receiving daily oral doses of 5 mg/kg/day or greater experienced unexpected CNS effects throughout the study. These effects occurred acutely and included marked sedation and apparent visual impairment which was characterized by a lack of awareness of objects, failure to fix on and follow moving objects, and absence of a blink reaction. Plasma exposures (AUCs) at 5 mg/kg/day were equal to those in humans receiving the maximum recommended daily human dose of 56 mg/day. The effects were reversible upon cessation of treatment and were not associated with any observed structural abnormality. The implications of these findings for humans are unknown.

Filmtab® - Film-sealed tablets, Abbott
Revised: August, 1999
Ref. 03-4957-R5
ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.

Shown in Product Identification Guide, page 303

GENGRAF™ Capsules ℞

[gĕn-grăf]
(cyclosporine capsules, USP [MODIFIED])
Rx only

> WARNING
>
> Only physicians experienced in the management of systemic immunosuppressive therapy for the indicated disease should prescribe Gengraf™ (cyclosporine capsules, USP [MODIFIED]). At doses used in solid organ transplantation, only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe Gengraf™. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.
>
> Gengraf™, a systemic immunosuppressant, may increase the susceptibility to infection and the development of neoplasia. In kidney, liver, and heart transplant patients Gengraf™ may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients.

> Gengraf™ (cyclosporine capsules, USP [MODIFIED]) has increased bioavailability in comparison to Sandimmune®* (cyclosporine capsules, USP [NON-MODIFIED]). Gengraf™ and Sandimmune®* are not bioequivalent and cannot be used interchangeably without physician supervision. For a given trough concentration, cyclosporine exposure will be greater with Gengraf™ than with Sandimmune®*. If a patient who is receiving exceptionally high doses of Sandimmune®* is converted to Gengraf™, particular caution should be exercised. Cyclosporine blood concentrations should be monitored in transplant and rheumatoid arthritis patients taking Gengraf™ to avoid toxicity due to high concentrations. Dose adjustments should be made in transplant patients to minimize possible organ rejection due to low concentrations. Comparison of blood concentrations in the published literature with blood concentrations obtained using current assays must be done with detailed knowledge of the assay methods employed.

> **For Psoriasis Patients (*see also Boxed WARNINGS above*)**
>
> Psoriasis patients previously treated with PUVA and to a lesser extent, methotrexate or other immunosuppressive agents, UVB, coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking Gengraf™ (cyclosporine capsules, USP [MODIFIED]).
>
> Cyclosporine, the active ingredient in Gengraf™, in recommended dosages, can cause systemic hypertension and nephrotoxicity. The risk increases with increasing dose and duration of cyclosporine therapy. Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine, and therefore, renal function must be monitored during therapy.

DESCRIPTION

Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is a modified oral formulation of cyclosporine that forms an aqueous dispersion in an aqueous environment.

NOTE: The nomenclature "Cyclosporine Capsules for Microemulsion" has been changed throughout the insert to read "Cyclosporine, Capsules USP [MODIFIED]".

Cyclosporine, the active principle in Gengraf™ Capsules, is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Aphanocladium album*.

Chemically, cyclosporine is designated as [R-[R*, R*-(E)]]-cyclic-(L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl-L-α-amino-butyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl).

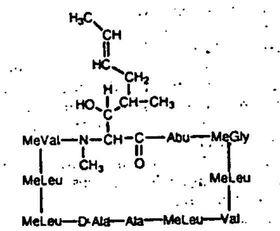
Gengraf™ Capsules (cyclosporine capsules, USP **[MODIFIED]**) are available in 25 mg and 100 mg strengths.

Each 25 mg capsule contains: cyclosporine, 25 mg, alcohol, USP, absolute, 12.8% v/v (10.1% wt/vol.).

Each 100 mg capsule contains: cyclosporine, 100 mg, alcohol, USP, absolute, 12.8% v/v (10.1% wt/vol.).

Inactive Ingredients: FD&C Blue No. 2, gelatin NF, polyethylene glycol NF, polyoxyl 35 castor oil NF, polysorbate 80 NF, propylene glycol USP, sorbitan monooleate NF, titanium dioxide.

The chemical structure for cyclosporine USP is:



$C_{62}H_{111}N_{11}O_{12}$ Mol. Wt. 1202.64

CLINICAL PHARMACOLOGY

Cyclosporine is a potent immunosuppressive agent that in animals prolongs survival of allogeneic transplants involving skin, kidney, liver, heart, pancreas, bone marrow, small intestine, and lung. Cyclosporine has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated immune reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft vs. host disease in many animal species for a variety of organs.

The effectiveness of cyclosporine results from specific and reversible inhibition of immunocompetent lymphocytes in the G_0- and G_1-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release including interleukin-2.

No effects on phagocytic function (changes in enzyme secretions, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) have been detected in animals. Cyclosporine does not cause bone marrow suppression in animal models or man.

Pharmacokinetics: The immunosuppressive activity of cyclosporine is primarily due to parent drug. Following oral administration, absorption of cyclosporine is incomplete. The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. Elimination of cyclosporine is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in urine. The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5 to 18 hours). Following intravenous administration, the blood clearance of cyclosporine (assay: HPLC) is approximately 5 to 7 mL/min/kg in adult recipients of renal or liver allografts. Blood cyclosporine clearance appears to be slightly slower in cardiac transplant patients.

The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear within the therapeutic dose range. The intersubject variability (total, % CV) of cyclosporine exposure (AUC) when cyclosporine (MODIFIED) or cyclosporine (NON-MODIFIED) is administered ranges from approximately 20% to 50% in renal transplant patients. This intersubject variability contributes to the need for individualization of the dosing regimen for optimal therapy (*see DOSAGE AND ADMINISTRATION*). Intrasubject variability of AUC in renal transplant recipients (% CV) was 9%–21% for cyclosporine

(MODIFIED) and 19%–26% for cyclosporine (NON-MODIFIED). In the same studies, intrasubject variability of trough concentrations (% CV) was 17%–30% for cyclosporine (MODIFIED) and 16%-38% for cyclosporine (NON-MODIFIED).

Absorption: Cyclosporine (MODIFIED) has increased bioavailability compared to cyclosporine (NON-MODIFIED). The absolute bioavailability of cyclosporine administered as Sandimmune®* (cyclosporine [NON-MODIFIED]) is dependent on the patient population, estimated to be less than 10% in liver transplant patients and as great as 89% in some renal transplant patients. The absolute bioavailability of cyclosporine administered as cyclosporine (MODIFIED) has not been determined in adults. In studies of renal transplant, rheumatoid arthritis and psoriasis patients, the mean cyclosporine AUC was approximately 20% to 50% greater and the peak blood cyclosporine concentration (C_{max}) was approximately 40% to 106% greater following administration of cyclosporine (MODIFIED) compared to following administration of cyclosporine (NON-MODIFIED). The dose normalized AUC in *de novo* liver transplant patients administered cyclosporine (MODIFIED) 28 days after transplantation was 50% greater and C_{max} was 90% greater than in those patients administered cyclosporine (NON-MODIFIED). AUC and C_{max} are also increased cyclosporine (MODIFIED) relative to cyclosporine (NON-MODIFIED) in heart transplant patients, but data are very limited. Although the AUC and C_{max} values are higher on cyclosporine (MODIFIED) relative to cyclosporine (NON-MODIFIED), the pre-dose trough concentrations (dose-normalized) are similar for the two formulations.

Following oral administration of cyclosporine (MODIFIED), the time to peak blood cyclosporine concentration (T_{max}) ranged from 1.5 to 2.0 hours. The administration of food with cyclosporine (MODIFIED) decreases the cyclosporine AUC and C_{max}. A high fat meal (669 kcal, 45 grams fat) consumed within one-half hour before cyclosporine (MODIFIED) administration decreased the AUC by 13% and C_{max} by 33%. The effects of a low fat meal (667 kcal, 15 grams fat) were similar.

The effect of T-tube diversion of bile on the absorption of cyclosporine from cyclosporine (MODIFIED) was investigated in eleven *de novo* liver transplant patients. When the patients were administered cyclosporine (MODIFIED) with and without T-tube diversion of bile, very little difference in absorption was observed, as measured by the change in maximal cyclosporine blood concentrations from pre-dose values with the T-tube closed relative to when it was open: 6.9±41% (range –55% to 68%).

[See first table above]

Distribution: Cyclosporine is distributed largely outside the blood volume. The steady state volume of distribution during intravenous dosing has been reported as 3–5 L/kg in solid organ transplant recipients. In blood, the distribution is concentration dependent. Approximately 33%–47% is in plasma, 4%–9% in lymphocytes, 5%–12% in granulocytes, and 41%–58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins. Cyclosporine is excreted in human milk (*see PRECAUTIONS, Nursing Mothers*).

Metabolism: Cyclosporine is extensively metabolized by the cytochrome P-450 III-A enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the coadministration of a variety of agents (*see PRECAUTIONS, Drug Interactions*). At least 25 metabolites have been identified from human bile, feces, blood, and urine. The biological activity of the metabolites and their contributions to toxicity are considerably less than those of the parent compound. The major metabolites (M1, M9, and M4N) result from oxidation at the 1-beta, 9-gamma, and 4-N-demethylated positions, respectively. At steady state following the oral administration of cyclosporine (NON-MODIFIED), the mean AUCs for blood concentrations of M1, M9 and M4N are about 70%, 21%, and 7.5% of the AUC for blood cyclosporine concentrations, respectively. Based on blood concentration data from stable renal transplant patients (13 patients administered cyclosporine (MODIFIED) and cyclosporine (NON-MODIFIED) in a crossover study), and bile concentration data from *de novo* liver transplant patients (4 administered cyclosporine (MODIFIED), 3 administered cyclosporine (NON-MODIFIED), the percentage of dose present as M1, M9, and M4N metabolites is similar when either cyclosporine (MODIFIED) or cyclosporine (NON-M DIFIED) is administered.

Excretion: Only 0.1% of a cyclosporine dose is excreted unchanged in the urine. Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Neither dialysis nor renal failure alter cyclosporine clearance significantly.

Drug Interactions: (*see PRECAUTIONS, Drug Interactions*). When diclofenac or methotrexate was co-administered with cyclosporine in rheumatoid arthritis patients, the AUC of diclofenac and methotrexate, each was significantly increased (*see PRECAUTIONS, Drug Interactions*). No clinically significant pharmacokinetic interactions occurred between cyclosporine and aspirin, ketoprofen, piroxicam, or indomethacin.

Special Population: ***Pediatric Population:*** Pharmacokinetic data from pediatric patients administered cyclosporine (MODIFIED) or cyclosporine (NON-MODIFIED) are very limited. In 15 renal transplant patients aged 3-16 years, cyclosporine whole blood clearance after IV administration of cyclosporine (NON-MODIFIED) was 10.6±3.7 mL/min/kg (assay: Cyclo-trac specific RIA). In a study of 7 renal transplant patients aged 2–16, the cyclosporine clearance ranged from 9.8 to 15.5 mL/min/kg. In 9 liver transplant patients aged 0.6 to 5.6 years, clearance was 9.3±5.4 mL/min/kg (assay: HPLC).

In the pediatric population, cyclosporine (MODIFIED) also demonstrates an increased bioavailability as compared to cyclosporine (NON-MODIFIED). In 7 liver *de novo* transplant patients aged 1.4 to 10 years, the absolute bioavailability of cyclosporine (MODIFIED) was 43% (range 30% to 68%) and for cyclosporine (NON-MODIFIED) in the same individuals absolute bioavailability was 28% (range 17% to 42%).

[See second table above]

Geriatric Population: Comparison of single dose data from both normal elderly volunteers (N=18, mean age 69 years) and elderly rheumatoid arthritis patients (N=16, mean age 68 years) to single dose data in young adult volunteers (N=16, mean age 26 years) showed no significant difference in the pharmacokinetic parameters.

Pharmacokinetic Parameters (mean ± SD)

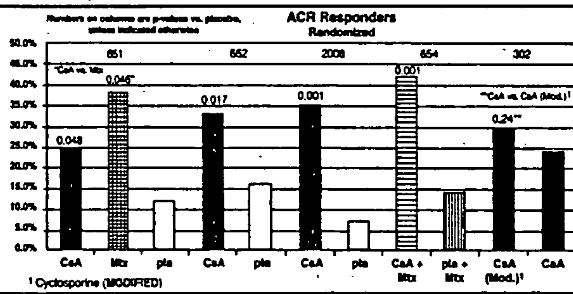
Patient Population	Dose/day[1] (mg/d)	Dose/weight (mg/kg/d)	AUC[2] (ng·hr/mL)	C_{max} (ng/mL)	Trough[3] (ng/mL)	CL/F (mL/min)	CL/F (mL/min/kg)
De novo renal transplant[4] Week 4 (N=37)	597±174	7.95±2.81	8772±2089	1802±428	361±129	593±204	7.8±2.9
Stable renal transplant[4] (N=55)	344±122	4.10±1.58	6035±2194	1333±469	251±116	492±140	5.9±2.1
De novo liver transplant[5] Week 4 (N=18)	458±190	6.89±3.68	7187±2816	1555±740	268±101	577±309	8.6±5.7
De novo rheumatoid arthritis[6] (N=23)	182±55.6	2.37±0.36	2641±877	728±263	96.4±37.7	613±196	8.3±2.8
De novo psoriasis[6] Week 4 (N=18)	189±69.8	2.48±0.65	2324±1048	655±186	74.9±46.7	723±186	10.2±3.9

[1]Total daily dose was divided into two doses administered every 12 hours.
[2]AUC was measured over one dosing interval.
[3]Trough concentration was measured just prior to the morning cyclosporine (MODIFIED) dose, approximately 12 hours after the previous dose.
[4]Assay: TDx specific monoclonal fluorescence polarization immunoassay.
[5]Assay: Cyclo-trac specific monoclonal radioimmunoassay.
[6]Assay: INCSTAR specific monoclonal radioimmunoassay.

Pediatric Pharmacokinetic Parameters (mean ± SD)

Patient Population	Dose/day (mg/d)	Dose/weight (mg/kg/d)	AUC[1] (ng·hr/mL)	C_{max} (ng/mL)	CL/F (mL/min)	CL/F (mL/min/kg)
Stable liver transplant[2]						
Age 2–8, Dosed TID (N=9)	101±25	5.95±1.32	2163±801	629±219	285±94	16.6±4.3
Age 8–15, Dosed BID (N=8)	188±55	4.96±2.09	4272±1462	975±281	378±80	10.2±4.0
Stable liver transplant[3]						
Age 3, Dosed BID (N=1)	120	8.33	5832	1050	171	11.9
Age 8–15, Dosed BID (N=5)	158±55	5.51±1.91	4452±2475	1013±635	328±121	11.0±1.9
Stable renal transplant[3]						
Age 7–15, Dosed BID (N=5)	328±83	7.37±4.11	6922±1988	1827±487	418±143	8.7±2.9

[1]AUC was measured over one dosing interval.
[2]Assay: Cyclo-trac specific monoclonal radioimmunoassay.
[3]Assay: TDx specific monoclonal fluorescence polarization immunoassay.



CLINICAL TRIALS

Rheumatoid Arthritis: The effectiveness of cyclosporine (NON-MODIFIED) and cyclosporine (MODIFIED) in the treatment of severe rheumatoid arthritis was evaluated in five clinical studies involving a total of 728 cyclosporine treated patients and 273 placebo treated patients.

A summary of the results is presented for the "responder" rates per treatment group, with a responder being defined as a patient having *completed* the trial with a 20% improvement in the tender and the swollen joint count and a 20% improvement in 2 of 4 of investigator global, patient global, disability, and erythrocyte sedimentation rates (ESR) for the Studies 651 and 652 and 3 of 5 of investigator global, patient global, disability, visual analog pain, and ESR for Studies 2008, 654, and 302.

Study 651 enrolled 264 patients with active rheumatoid arthritis with at least 20 involved joints, who had failed at least one major RA drug, using a 3:3:2 randomization to one of the following three groups: (1) cyclosporine dosed at 2.5–5 mg/kg/day, (2) methotrexate at 7.5–15 mg/week, or (3) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 3.1 mg/kg/day. See Graph below.

Study 652 enrolled 250 patients with active RA with >6 active painful or tender joints who had failed at least one major RA drug. Patients were randomized using a 3:3:2 randomization to 1 of 3 treatment arms: (1) 1.5–5 mg/kg/day of cyclosporine, (2) 2.5–5 mg/kg/day of cyclosporine, and (3) placebo. Treatment duration was 16 weeks. The mean cyclosporine dose for group 2 at the last visit was 2.92 mg/kg/day. See Graph below.

Study 2008 enrolled 144 patients with active RA and >6 active joints who had unsuccessful treatment courses of aspirin and gold or Penicillamine. Patients were randomized to one of two treatment groups: (1) cyclosporine 2.5–5 mg/kg/day with adjustments after the first month to achieve a target trough level and (2) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 3.63 mg/kg/day. See Graph below.

Study 654 enrolled 148 patients who remained with active joint counts of 6 or more despite treatment with maximally tolerated methotrexate doses for at least three months. Patients continued to take their current dose of methotrexate and were randomized to receive, in addition, one of the following medications: (1) cyclosporine 2.5 mg/kg/day with dose increases of 0.5 mg/kg/day at weeks 2 and 4 if there was no evidence of toxicity and further increases of 0.5 mg/kg/day at weeks 8 and 16 if a <30% decrease in active joint count occurred without any significant toxicity; dose decreases could be made at any time for toxicity or (2) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 2.8 mg/kg/day (range: 1.3-4.1). See Graph below.

Continued on next page

Gengraf—Cont.

Study 302 enrolled 299 patients with severe active RA, 99% of whom were unresponsive or intolerant to at least one prior major RA drug. Patients were randomized to 1 of 2 treatment groups (1) cyclosporine (MODIFIED) and (2) cyclosporine (NON-MODIFIED), both of which were started at 2.5 mg/kg/day and increased after 4 weeks for inefficacy in increments of 0.5 mg/kg/day to a maximum of 5 mg/kg/day and decreased at any time for toxicity. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 2.91 mg/kg/day (range: 0.72-5.17) for cyclosporine (MODIFIED) and 3.27 mg/kg/day (range: 0.73-5.68) for cyclosporine (NON-MODIFIED). See Graph below.

[See graphic on previous page third from top]

INDICATIONS AND USAGE

Kidney, Liver and Heart Transplantation: Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine (MODIFIED) has been used in combination with azathioprine and corticosteroids.

Rheumatoid Arthritis: Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is indicated for the treatment of patients with severe active, rheumatoid arthritis where the disease has not adequately responded to methotrexate. Gengraf™ can be used in combination with methotrexate in rheumatoid arthritis patients who do not respond adequately to methotrexate alone.

Psoriasis: Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is indicated for the treatment of *adult, nonimmunocompromised* patients with severe (i.e., extensive and/or disabling), recalcitrant, plaque psoriasis who have failed to respond to at least one systemic therapy (e.g., PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated.

While rebound rarely occurs, most patients will experience relapse with Gengraf™ as with other therapies upon cessation of treatment.

CONTRAINDICATIONS

General: Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

Rheumatoid Arthritis: Rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension or malignancies should not receive Gengraf™ (cyclosporine capsules, USP [MODIFIED]).

Psoriasis: Psoriasis patients who are treated with Gengraf™ (cyclosporine capsules, USP [MODIFIED]) should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy. Psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Gengraf™.

WARNINGS

(*see also Boxed WARNINGS*). **All Patients:** Cyclosporine, the active ingredient of Gengraf™ (cyclosporine capsules, USP [MODIFIED]), can cause nephrotoxicity and hepatotoxicity. The risk increases with increasing doses of cyclosporine. Renal dysfunction including structural kidney damage is a potential consequence of Gengraf™ and therefore renal function must be monitored during therapy. **Care should be taken in using cyclosporine with nephrotoxic drugs (see *PRECAUTIONS*).**

Patients receiving Gengraf™ require frequent monitoring of serum creatinine (*see Special Monitoring under DOSAGE AND ADMINISTRATION*). Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can be associated with the occurrence of structural kidney damage and persistent renal dysfunction.

An increase in serum creatinine and BUN may occur during Gengraf™ therapy and reflect a reduction in the glomerular filtration rate. Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

Because Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is not bioequivalent to Sandimmune®* (cyclosporine [NON-MODIFIED]), conversion from Gengraf™ to Sandimmune®* (cyclosporine [NON-MODIFIED]) using a 1:1 ratio (mg/kg/day) may result in lower cyclosporine blood concentrations. Conversion from Gengraf™ to Sandimmune®* (cyclosporine [NON-MODIFIED]) should be made with increased monitoring to avoid the potential of underdosing.

Kidney, Liver, and Heart Transplant: Cyclosporine, the active ingredient of Gengraf™ (cyclosporine capsules, USP [MODIFIED]), can cause nephrotoxicity and hepatotoxicity when used in high doses. It is not unusual for serum creatinine and BUN levels to be elevated during cyclosporine therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

Based on the historical cyclosporine (NON-MODIFIED) experience with oral solution, nephrotoxicity associated with cyclosporine had been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted 2–3 months after renal transplant and consisted of an arrest in the fall of the pre-operative elevations of BUN and creatinine at a range of 35–45 mg/dL and 2.0–2.5 mg/dL respectively. These elevations were often responsive to cyclosporine dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to renal rejection episodes, care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to cyclosporine dosage reduction.

Although specific diagnostic criteria which reliably differentiate renal graft rejection from drug toxicity have not been found, a number of parameters have been significantly associated with one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

[See table below]

Nephrotoxicity vs. Rejection

Parameter	Nephrotoxicity	Rejection
History	Donor > 50 years old or hypotensive Prolonged kidney preservation Prolonged anastomosis time Concomitant nephrotoxic drugs	Anti-donor immune response Retransplant patient
Clinical	Often > 6 weeks postop[b] Prolonged initial nonfunction (acute tubular necrosis)	Often < 4 weeks postop[b] Fever > 37.5°C Weight gain > 0.5 kg Graft swelling and tenderness Decrease in daily urine volume > 500 mL (or 50%)
Laboratory	CyA serum trough level > 200 ng/mL Gradual rise in Cr (< 0.15 mg/dL/day)[a] Cr plateau < 25% above baseline BUN/Cr ≥ 20	CyA serum trough level < 150 ng/mL Rapid rise in Cr (> 0.3 mg/dL/day)[a] Cr > 25% above baseline BUN/Cr < 20
Biopsy	Arteriolopathy (medial hypertrophy[a], hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring) Tubular atrophy, isometric vacuolization, isolated calcifications Minimal edema Mild focal infiltrates[c] Diffuse interstitial fibrosis, often striped form	Endovasculitis[c] (proliferation[a], intimal arteritis[b], necrosis, sclerosis) Tubulitis with RBC[b] and WBC[b] casts, some irregular vacuolization Interstitial edema[c] and hemorrhage[b] Diffuse moderate to severe mononuclear infiltrates[d] Glomerulitis (mononuclear cells)[c]
Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine isometric vacuolization of tubular cells	Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells These strongly express HLA-DR antigens
Urine Cytology	Tubular cells with vacuolization and granularization	Degenerative tubular cells, plasma cells, and lymphocyturia > 20% of sediment
Manometry Ultrasonography	Intracapsular pressure < 40 mm Hg[b] Unchanged graft cross sectional area	Intracapsular pressure > 40 mm Hg[b] Increase in graft cross sectional area AP diameter ≥ Transverse diameter
Magnetic Resonance Imagery	Normal appearance	Loss of distinct corticomedullary junction, swelling image intensity of parachyma approaching that of psoas, loss of hilar fat
Radionuclide Scan	Normal or generally decreased perfusion Decrease in tubular function (^{131}I-hippuran) > decrease in perfusion (^{99m}Tc DTPA)	Patchy arterial flow Decrease in perfusion > decrease in tubular function Increased uptake of Indium 111 labeled platelets or Tc-99m in colloid
Therapy	Responds to decreased cyclosporine	Responds to increased steroids or antilymphocyte globulin

[a]p < 0.05, [b]p < 0.01, [c]p < 0.001, [d]p < 0.0001

A form of a cyclosporine-associated nephropathy is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5% to 15% of transplant recipients who have received cyclosporine will fail to show a reduction in rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate one or several of the following alterations: tubular vacuolization, tubular microcalcifications, peritubular capillary congestion, arteriolopathy, and a striped form of interstitial fibrosis with tubular atrophy. Though none of these morphologic changes is entirely specific, a diagnosis of cyclosporine-associated structural nephrotoxicity requires evidence of these findings.

When considering the development of cyclosporine-associated nephropathy, it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough levels of cyclosporine. This is particularly true during the first 6 post-transplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients are prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined. Reversibility of arteriolopathy has been reported after stopping cyclosporine or lowering the dosage.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated.

In the event of severe and unremitting rejection, when rescue therapy with pulse steroids and monoclonal antibodies fail to reverse the rejection episode, it may be preferable to switch to alternative immunosuppressive therapy rather than increase the Gengraf™ dose to excessive levels.

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans (*see ADVERSE REACTIONS*).

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity associated with cyclosporine use had been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of cyclosporine were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

As in patients receiving other immunosuppressants, those patients receiving cyclosporine are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system resulting in increased risk of infection or malignancy, a treatment regimen containing multiple immunosuppressants should be used with caution.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Care should be taken in using cyclosporine with nephrotoxic drugs (*see PRECAUTIONS*).

Rheumatoid Arthritis: Cyclosporine nephropathy was detected in renal biopsies of six out of 60 (10%) rheumatoid

Antibiotics	Antineoplastics	Anti-inflammatory Drugs	Gastrointestinal Agents
gentamicin	melphalan	azapropazon	cimetidine
tobramycin		diclofenac	ranitidine
vancomycin	*Antifungals*	naproxen	
trimethoprim with sulfamethoxazole	amphotericin B	sulindac	*Immunosuppressives*
	ketoconazole		tacrolimus

months. Only one patient, out of these 6 patients, was treated with a dose ≤4 mg/kg/day. Serum creatinine improved in all but one patient after discontinuation of cyclosporine. The "maximal creatinine increase" appears to be a factor in predicting cyclosporine nephropathy.

There is a potential, as with other immunosuppressive agents, for an increase in the occurrence of malignant lymphomas with cyclosporine. It is not clear whether the risk with cyclosporine is greater than that in Rheumatoid Arthritis patients or in Rheumatoid Arthritis patients on cytotoxic treatment for this indication. Five cases of lymphoma were detected: four in a survey of approximately 2,300 patients treated with cyclosporine for rheumatoid arthritis, and another case of lymphoma was reported in a clinical trial. Although other tumors (12 skin cancers, 24 solid tumors of diverse types, and 1 multiple myeloma) were also reported in this survey, epidemiologic analyses did not support a relationship to cyclosporine other than for malignant lymphomas.

Patients should be thoroughly evaluated before and during Gengraf™ (cyclosporine capsules, USP [MODIFIED]) treatment for the development of malignancies. Moreover, use of Gengraf™ therapy with other immunosuppressive agents may induce an excessive immunosuppression which is known to increase the risk of malignancy.

Psoriasis: (*see also Boxed WARNINGS for Psoriasis*). Since cyclosporine is a potent immunosuppressive agent with a number of potentially serious side effects, the risks and benefits of using Gengraf™ (cyclosporine capsules, USP [MODIFIED]) should be considered before treatment of patients with psoriasis. Cyclosporine, the active ingredient in Gengraf™, can cause nephrotoxicity and hypertension (*see PRECAUTIONS*) and the risk increases with increasing dose and duration of therapy. Patients who may be at increased risk such as those with abnormal renal function, uncontrolled hypertension or malignancies, should not receive Gengraf™.

Renal dysfunction is a potential consequence of Gengraf™, therefore renal function must be monitored during therapy. Patients receiving Gengraf™ require frequent monitoring of serum creatinine (*see Special Monitoring under DOSAGE AND ADMINISTRATION*). Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can cause structural kidney damage and persistent renal dysfunction.

An increase in serum creatinine and BUN may occur during Gengraf™ therapy and reflects a reduction in the glomerular filtration rate.

Kidney biopsies from 86 psoriasis patients treated for a mean duration of 23 months with 1.2–7.6 mg/kg/day of cyclosporine showed evidence of cyclosporine nephropathy in 18/86 (21%) of the patients. The pathology consisted of renal tubular atrophy and interstitial fibrosis. On repeat biopsy of 13 of these patients maintained on various dosages of cyclosporine for a mean of 2 additional years, the number with cyclosporine induced nephropathy rose to 26/86 (30%). The majority of patients (19/26) were on a dose of ≥5.0 mg/kg/day (the highest recommended dose is 4 mg/kg/day). The patients were also on cyclosporine for greater than 15 months (18/26) and/or had a clinically significant increase in serum creatinine for greater than 1 month (21/26). Creatinine levels returned to normal range in 7 of 11 patients in whom cyclosporine therapy was discontinued.

There is an increased risk for the development of skin and lymphoproliferative malignancies in cyclosporine-treated psoriasis patients. The relative risk of malignancies is comparable to that observed in psoriasis patients treated with other immunosuppressive agents.

Tumors were reported in 32 (2.2%) of 1439 psoriasis patients treated with cyclosporine worldwide from clinical trials. Additional tumors have been reported in 7 patients in cyclosporine postmarketing experience. Skin malignancies were reported in 16 (1.1%) of these patients; all but 2 of them had previously received PUVA therapy. Methotrexate was received by 7 patients. UVB and coal tar have been used by 2 and 3 patients, respectively. Seven patients had either a history of previous skin cancer or a potentially predisposing lesion was present prior to cyclosporine exposure. Of the 16 patients with skin cancer, 11 patients had 18 squamous cell carcinomas and 7 patients had 10 basal cell carcinomas.

There were two lymphoproliferative malignancies; one case of non-Hodgkin's lymphoma which required chemotherapy, and one case of mycosis fungoides which regressed spontaneously upon discontinuation of cyclosporine. There were four cases of benign lymphocytic infiltration: 3 regressed spontaneously upon discontinuation of cyclosporine, while the fourth regressed despite continuation of the drug. The remainder of the malignancies, 13 cases (0.9%), involved various organs.

Patients should not be treated concurrently with cyclosporine and PUVA or UVB, other radiation therapy, or other immunosuppressive agents, because of the possibility of excessive immunosuppression and the subsequent risk of malignancies (*see CONTRAINDICATIONS*). Patients should also be warned to protect themselves appropriately when in the sun, and to avoid excessive sun exposure. Patients should be thoroughly evaluated before and during treatment for the presence of malignancies remembering that malignant lesions may be hidden by psoriatic plaques. Skin lesions not typical of psoriasis should be biopsied before starting treatment. Patients should be treated with Gengraf™ (cyclosporine capsules, USP [MODIFIED]) only after complete resolution of suspicious lesions, and only if there are no other treatment options (*see Special Monitoring for Psoriasis Patients*).

PRECAUTIONS

General: ***Hypertension:*** Cyclosporine is the active ingredient of Gengraf™ (cyclosporine capsules, USP [MODIFIED]). Hypertension is a common side effect of cyclosporine therapy which may persist (*see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION for monitoring recommendations*). Mild or moderate hypertension is encountered more frequently than severe hypertension and the incidence decreases over time. In recipients of kidney, liver, and heart allografts treated with cyclosporine, antihypertensive therapy may be required (*see Special Monitoring of Rheumatoid Arthritis and Psoriasis Patients*). However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. While calcium antagonists can be effective agents in treating cyclosporine-associated hypertension, they can interfere with cyclosporine metabolism (*see PRECAUTIONS, Drug Interactions*).

Vaccination: During treatment with cyclosporine, vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

Special Monitoring of Rheumatoid Arthritis Patients: Before initiating treatment, a careful physical examination, including blood pressure measurements (on at least two occasions) and two creatinine levels to estimate baseline should be performed. Blood pressure and serum creatinine should be evaluated every 2 weeks during the initial 3 months and then monthly if the patient is stable. It is advisable to monitor serum creatinine and blood pressure always after an increase of the dose of nonsteroidal anti-inflammatory drugs and after initiation of new nonsteroidal anti-inflammatory drug therapy during Gengraf™ (cyclosporine capsules, USP [MODIFIED]) treatment. If co-administered with methotrexate, CBC and liver function tests are recommended to be monitored monthly (*see also PRECAUTIONS, General, Hypertension*).

In patients who are receiving cyclosporine, the dose of Gengraf™ should be decreased by 25%–50% if hypertension occurs. If hypertension persists, the dose of Gengraf™ should be further reduced or blood pressure should be controlled with antihypertensive agents. In most cases, blood pressure has returned to baseline when cyclosporine was discontinued.

In placebo-controlled trials of rheumatoid arthritis patients, systolic hypertension (defined as an occurrence of two systolic blood pressure readings >140 mmHg) and diastolic hypertension (defined as two diastolic blood pressure readings >90 mmHg) occurred in 33% and 19% of patients treated with cyclosporine, respectively. The corresponding placebo rates were 22% and 8%.

Special Monitoring for Psoriasis Patients: Before initiating treatment, a careful dermatological and physical examination, including blood pressure measurements (on at least two occasions) should be performed. Since Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is an immunosuppressive agent, patients should be evaluated for the presence of occult infection on their first physical examination and for the presence of tumors initially, and throughout treatment with Gengraf™. Skin lesions not typical for psoriasis should be biopsied before starting Gengraf™. Patients with malignant or premalignant changes of the skin should be treated with Gengraf™ only after appropriate treatment of such lesions and if no other treatment option exists.

Baseline laboratories should include serum creatinine (on two occasions), BUN, CBC, serum magnesium, potassium, uric acid, and lipids.

The risk of cyclosporine nephropathy is reduced when the starting dose is low (2.5 mg/kg/day), the maximum dose does not exceed 4.0 mg/kg/day, serum creatinine is monitored regularly while cyclosporine is administered, and the dose of Gengraf™ is decreased when the rise in creatinine is greater than or equal to 25% above the patients pretreatment level. The increase in creatinine is generally reversible upon timely decrease of the dose of Gengraf™ or its discontinuation.

Serum creatinine and BUN should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable. If the serum creatinine is greater than or equal to 25% above the patient's pretreatment level, serum creatinine should be repeated within two weeks. If the change in serum creatinine remains greater than or equal to 25% above baseline, Gengraf™ should be reduced by 25%–50%. If at any time the serum creatinine increases by greater than or equal to 50% above pretreatment level, Gengraf™ should be reduced by 25%–50%. Gengraf™ should be discontinued if reversibility (within 25% of baseline) of serum creatinine is not achievable after two dosage modifications. It is advisable to monitor serum creatinine after an increase of the dose of nonsteroidal anti-inflammatory drug and after initiation of new nonsteroidal anti-inflammatory therapy during Gengraf™ treatment.

Blood pressure should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable, or more frequently when dosage adjustments are made. Patients without a history of previous hypertension before initiation of treatment with Gengraf™, should have the drug reduced by 25%-50% if found to have sustained hypertension. If the patient continues to be hypertensive despite multiple reductions of Gengraf™, then Gengraf™ should be discontinued. For patients with treated hypertension, before the initiation of Gengraf™ therapy, their medication should be adjusted to control hypertension while on Gengraf™. Gengraf™ should be discontinued if a change in hypertension management is not effective or tolerable.

CBC, uric acid, potassium, lipids, and magnesium should also be monitored every 2 weeks for the first 3 months of therapy, and then monthly if the patient is stable or more frequently when dosage adjustments are made. Gengraf™ dosage should be reduced by 25%–50% for any abnormality of clinical concern.

In controlled trials of cyclosporine in psoriasis patients, cyclosporine blood concentrations did not correlate well with either improvement or with side effects such as renal dysfunction.

Information for Patients: Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving cyclosporine. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasia. Patients should also be informed of the risk of hypertension and renal dysfunction.

Patients should be advised that during treatment with cyclosporine, vaccination may be less effective and the use of live attenuated vaccines should be avoided.

Patients should be advised to take Gengraf™ on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

Laboratory Tests: In all patients treated with cyclosporine, renal and liver functions should be assessed repeatedly by measurement of serum creatinine, BUN, serum bilirubin, and liver enzymes. Serum lipids, magnesium, and potassium should also be monitored. Cyclosporine blood concentrations should be routinely monitored in transplant patients (*see DOSAGE AND ADMINISTRATION, Blood Concentration Monitoring in Transplant Patients*), and periodically monitored in rheumatoid arthritis patients.

Drug Interactions: All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

Drugs That May Potentiate Renal Dysfunction

[See table above]

Drugs That Alter Cyclosporine Concentrations: Cyclosporine is extensively metabolized. Cyclosporine concentrations may be influenced by drugs that affect microsomal enzymes, particularly cytochrome P-450 III-A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate Gengraf™ (cyclosporine capsules, USP [MODIFIED]) dosage adjustment are essential when these drugs are used concomitantly (*see DOSAGE AND ADMINISTRATION, Blood Concentration Monitoring*).

Drugs That Increase Cyclosporine Concentrations

Calcium Channel Blockers	Antibiotics	Other Drugs
diltiazem	clarithromycin	allopurinol
nicardipine	erythromycin	bromocriptine
verapamil		danazol
Antifungals	*Glucocorticoids*	metoclopramide
fluconazole	methylprednisolone	
itraconazole		
ketoconazole		

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 III-A and increase the concentrations of drugs metabolized by the cytochrome P-450 system. The interaction between HIV protease inhibitors and cyclosporine has not been studied. Care should be exercised when these drugs are administered concomitantly.

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

Continued on next page

G ngraf—Cont.

Drugs That Decrease Cyclosporine Concentrations

Antibiotics	*Anticonvulsants*	*Other Drugs*
nafcillin	carbamazepine	octreotide
rifampin	phenobarbital	ticlopidine
	phenytoin	

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

Nonsteroidal Anti-Inflammatory Drug (NSAID) Interactions: Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients (*see WARNINGS*).

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and (*p*-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Methotrexate Interaction: Preliminary data indicate that when methotrexate and cyclosporine were co-administered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

Other Drug Interactions: Reduced clearance of prednisolone, digoxin, and lovastatin has been observed when these drugs are administered with cyclosporine. In addition, a decrease in the apparent volume of distribution of digoxin has been reported after cyclosporine administration. Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. Myositis has occurred with concomitant lovastatin, frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone.

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. Doses used in the mouse and rat studies were 0.01 to 0.16 times the clinical maintenance dose (6 mg/kg). The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. Published reports indicate the co-treatment of hairless mice with UV irradiation and cyclosporine or other immunosuppressive agents shorten the time to skin tumor formation compared to UV irradiation alone.

Cyclosporine was not mutagenic in appropriate test systems. Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE), at high concentrations in this system.

No impairment in fertility was demonstrated in studies in male and female rats.

Widely distributed papillomatosis of the skin was observed after chronic treatment of dogs with cyclosporine at 9 times the human initial psoriasis treatment dose of 2.5 mg/kg, where doses are expressed on a body surface area basis. This papillomatosis showed a spontaneous regression upon discontinuation of cyclosporine.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants and patients with rheumatoid arthritis and psoriasis. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies in cyclosporine recipients is higher than in the normal, healthy population but similar to that in patients receiving other immunosuppressive therapies. Reduction or discontinuance of immunosuppression may cause the lesions to regress.

... development of malig-

Body System	Adverse Reactions	Randomized Kidney Patients: Cyclosporine (NON-MODIFIED) (N=227) %	Randomized Kidney Patients: Azathioprine (N=228) %	Cyclosporine Patients Cyclosporine, (NON-MODIFIED): Kidney (N=705) %	Heart (N=112) %	Liver (N=75) %
Genitourinary	Renal Dysfunction	32	6	25	38	37
Cardiovascular	Hypertension	26	18	13	53	27
	Cramps	4	<1	2	<1	0
Skin	Hirsutism	21	<1	21	28	45
	Acne	6	8	2	2	1
Central Nervous System	Tremor	12	0	21	31	55
	Convulsions	3	1	1	4	5
	Headache	2	<1	2	15	4
Gastrointestinal	Gum Hyperplasia	4	0	9	5	16
	Diarrhea	3	<1	3	4	8
	Nausea/Vomiting	2	<1	4	10	4
	Hepatotoxicity	<1	<1	4	7	4
	Abdominal Discomfort	<1	0	<1	7	0
Autonomic Nervous System	Paresthesia	3	0	1	2	1
	Flushing	<1	0	4	0	4
Hematopoietic	Leukopenia	2	19	<1	6	0
	Lymphoma	<1	0	1	6	1
Respiratory	Sinusitis	<1	0	4	3	7
Miscellaneous	Gynecomastia	<1	0	<1	4	3

Infectious Complications in Historical Randomized Studies in Renal Transplant Patients Using Cyclosporine (NON-MODIFIED)

Complication	Cyclosporine Treatment (N=227) % of Complications	Azathioprine with Steroids* (N=228) % of Complications
Septicemia	5.3	4.8
Abscesses	4.4	5.3
Systemic Fungal Infection	2.2	3.9
Local Fungal Infection	7.5	9.6
Cytomegalovirus	4.8	12.3
Other Viral Infections	15.9	18.4
Urinary Tract Infections	21.1	20.2
Wound and Skin Infections	7.0	10.1
Pneumonia	6.2	9.2

*Some patients also received ALG.

WARNINGS). Skin lesions not typical for psoriasis should be biopsied before starting cyclosporine treatment. Patients with malignant or premalignant changes of the skin should be treated with cyclosporine only after appropriate treatment of such lesions and if no other treatment option exists.

Pregnancy: ***Pregnancy Category C.*** Cyclosporine was not teratogenic in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. Cyclosporine has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the transplant doses in humans of 6.0 mg/kg, where dose corrections are based on body surface area. Cyclosporine was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardation.

There are no adequate and well-controlled studies in pregnant women. Gengraf™ (cyclosporine capsules, USP [MODIFIED]) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Pre-term delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. Therefore, the risks and benefits of using Gengraf™ during pregnancy should be carefully weighed.

Because of the possible disruption of maternal-fetal interaction, the risk/benefit ratio of using Gengraf™ in psoriasis patients during pregnancy should carefully be weighed with serious consideration for discontinuation of Gengraf™.

Nursing Mothers: Since cyclosporine is excreted in human milk, breast-feeding should be avoided.

Pediatric Use: Although no adequate and well-controlled studies have been completed in children, transplant recipients as young as one year of age have received cyclosporine (MODIFIED) with no unusual adverse effects. The safety and efficacy of cyclosporine (MODIFIED) treatment in pediatric patients with juvenile rheumatoid arthritis or psoriasis below the age of 18 have not been established.

Geriatric Use: In rheumatoid arthritis clinical trials with cyclosporine, 17.5% of patients were age 65 or older. These patients were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises ≥50% above the baseline after 3–4 months of therapy.

ADVERSE REACTIONS

Kidney, Liver, and Heart Transplantation: The principal ... renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure. The pathologic changes resembled those seen in the hemolytic-uremic syndrome and include thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed post-transplantation.

Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine appear to be related to the neurological manifestations of cyclosporine toxicity.

In controlled studies, the nature, severity and incidence of the adverse events that were observed in 493 transplanted patients treated with cyclosporine (MODIFIED) were comparable with those observed in 208 transplanted patients who received cyclosporine (NON-MODIFIED) in these same studies when the dosage of the two drugs was adjusted to achieve the same cyclosporine blood trough concentrations.

Based on the historical experience with cyclosporine (NON-MODIFIED), the following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants.

[See first table above]

Among 705 kidney transplant patients treated with cyclosporine oral solution (NON-MODIFIED) in clinical trials, the reason for treatment discontinuation was renal toxicity in 5.4%, infection in 0.9%, lack of efficacy in 1.4%, acute tubular necrosis in 1.0%, lymphoproliferative disorders in 0.3%, hypertension in 0.3%, and other reasons in 0.7% of the patients.

The following reactions occurred in 2% or less of cyclosporine (NON-MODIFIED)-treated patients: allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

The following reactions occurred rarely: anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

[See second table above]

Rheumatoid Arthritis: The principal adverse reactions associated with the use of cyclosporine in rheumatoid arthritis are renal dysfunction (see *WARNINGS*), hypertension (see *PRECAUTIONS*), headache, gastrointestinal disturbances and hirsutism/hypertrichosis.

Cyclosporine (MODIFIED)/Cyclosporine (NON-MODIFIED) Rheumatoid Arthritis
Percentage of Patients with Adverse Events ≥3% in any Cyclosporine Treated Group

		Studies 651 + 652 + 2008	Study 302	Study 654	Study 654	Study 302	Studies 651 + 652 + 2008
Body System	Preferred Term	Cyclosporine (NON-MODIFIED)† (N=269)	Cyclosporine (NON-MODIFIED) (N=155)	Methotrexate & Cyclosporine (NON-MODIFIED) (N=74)	Methotrexate & Placebo (N=73)	Cyclosporine (MODIFIED) (N=143)	Placebo (N=201)
Autonomic Nervous System Disorders	Flushing	2%	2%	3%	0%	5%	2%
Body As A Whole - General Disorders	Accidental Trauma	0%	1%	10%	4%	4%	0%
	Edema NOS*	5%	14%	12%	4%	10%	<1%
	Fatigue	6%	3%	8%	12%	3%	7%
	Fever	2%	3%	0%	0%	2%	4%
	Influenza-like symptoms	<1%	6%	1%	0%	3%	2%
	Pain	6%	9%	10%	15%	13%	4%
	Rigors	1%	1%	4%	0%	3%	1%
Cardiovascular Disorders	Arrhythmia	2%	5%	5%	6%	2%	1%
	Chest Pain	4%	5%	1%	1%	6%	1%
	Hypertension	8%	26%	16%	12%	25%	2%
Central and Peripheral Nervous System Disorders	Dizziness	8%	6%	7%	3%	8%	3%
	Headache	17%	23%	22%	11%	25%	9%
	Migraine	2%	3%	0%	0%	3%	1%
	Parethesia	8%	7%	8%	4%	11%	1%
	Tremor	8%	7%	7%	3%	13%	4%
Gastrointestinal System Disorders	Abdominal Pain	15%	15%	15%	7%	15%	10%
	Anorexia	3%	3%	1%	0%	3%	3%
	Diarrhea	12%	12%	18%	15%	13%	8%
	Dyspepsia	12%	12%	10%	8%	8%	4%
	Flatulence	5%	5%	5%	4%	4%	1%
	Gastrointestinal Disorder NOS*	0%	2%	1%	4%	4%	0%
	Gingivitis	4%	3%	0%	0%	0%	1%
	Gum Hyperplasia	2%	4%	1%	3%	4%	1%
	Nausea	23%	14%	24%	15%	18%	14%
	Rectal Hemorrhage	0%	3%	0%	0%	1%	1%
	Stomatitis	7%	5%	16%	12%	6%	8%
	Vomiting	9%	8%	14%	7%	6%	5%
Hearing and Vestibular Disorders	Eat Disorders NOS*	0%	5%	0%	0%	1%	0%
Metabolic and Nutritional Disorders	Hypomagnesemia	0%	4%	0%	0%	6%	0%
Musculoskeletal System Disorders	Arthropathy	0%	5%	0%	1%	4%	0%
	Leg Cramps/Involuntary Muscle Contractions	2%	11%	11%	3%	12%	1%
Psychiatric Disorders	Depression	3%	6%	3%	1%	1%	2%
	Insomnia	4%	1%	1%	0%	3%	2%
Renal	Creatinine elevations ≥30%	43%	39%	55%	19%	48%	13%
	Creatinine elevations ≥50%	24%	18%	26%	8%	18%	3%
Reproductive Disorders, Female	Leukorrhea	1%	0%	4%	0%	1%	0%
	Menstrual Disorder	3%	2%	1%	0%	1%	1%
Respiratory System Disorders	Bronchitis	1%	3%	1%	0%	1%	3%
	Coughing	5%	3%	5%	7%	4%	4%
	Dyspnea	5%	1%	3%	3%	1%	2%
	Infection NOS*	9%	5%	0%	7%	3%	10%
	Pharyngitis	3%	5%	5%	6%	4%	4%
	Pneumonia	1%	0%	4%	0%	1%	1%
	Rhinitis	0%	3%	11%	10%	1%	0%
	Sinusitis	4%	4%	8%	4%	3%	3%
	Upper Respiratory Tract	0%	14%	23%	15%	13%	0%
Skin and Appendages Disorders	Alopecia	3%	0%	1%	1%	4%	4%
	Bullous Eruption	1%	0%	4%	1%	1%	1%
	Hypertrichosis	19%	17%	12%	0%	15%	3%
	Rash	7%	12%	10%	7%	8%	10%
	Skin Ulceration	1%	1%	3%	4%	0%	2%
Urinary System Disorders	Dysuria	0%	0%	11%	3%	1%	2%
	Micturition Frequency	2%	4%	3%	1%	2%	2%
	NPN, Increased	0%	19%	12%	0%	18%	0%
	Urinary Tract Infection	0%	3%	5%	4%	3%	0%
Vascular (Extracardiac) Disorders	Purpura	3%	4%	1%	1%	2%	0%

†Includes patients in 2.5 mg/kg/day dose group only. *NOS = Not Otherwise Specified.

In rheumatoid arthritis patients treated in clinical trials within the recommended dose range, cyclosporine therapy was discontinued in 5.3% of the patients because of hypertension and in 7% of the patients because of increased creatinine. These changes are usually reversible with timely dose decrease or drug discontinuation. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

The following adverse events occurred in controlled clinical trials:

[See table above]

In addition, the following adverse events have been reported in 1% to <3% of the rheumatoid arthritis patients in the cyclosporine treatment group in controlled clinical trials.

Autonomic Nervous System: dry mouth, increased sweating;

Body as a Whole: allergy, asthenia, hot flushes, malaise, overdose, procedure NOS*, tumor NOS*, weight decrease, weight increase;

Cardiovascular: abnormal heart sounds, cardiac failure, myocardial infarction, peripheral ischemia;

Central and Peripheral Nervous System: hypoesthesia, neuropathy, vertigo;

Endocrine: goiter;

Gastrointestinal: constipation, dysphagia, enanthema, eructation, esophagitis, gastric ulcer, gastritis, gastroenteritus, gingival bleeding, glossitis, peptic ulcer, salivary gland enlargement, tongue disorder, tooth disorder;

Infection: abscess, bacterial infection, cellulitis, folliculitis, fungal infection, herpes simplex, herpes zoster, renal abscess, moniliasis, tonsillitis, viral infection;

Hematologic: anemia, epistaxis, leukopenia, lymphadenopathy;

Liver and Biliary System: bilirubinemia;

Metabolic and Nutritional: diabetes mellitus, hyperkalemia, hyperuricemia, hypoglycemia;

Musculoskeletal System: arthralgia, bone fracture, bursitis, joint dislocation, myalgia, stiffness, synovial cyst, tendon disorder;

Neoplasms: breast fibroadenosis, carcinoma;

Psychiatric: anxiety, confusion, decreased libido, emotional lability, impaired concentration, increased libido, nervousness, paroniria, somnolence;

Reproductive (Female): breast pain, uterine hemorrhage;

Respiratory System: abnormal chest sounds, bronchospasm;

Skin and Appendages: abnormal pigmentation, angioedema, dermatitis, dry skin, eczema, nail disorder, pruritus, skin disorder, urticaria;

Special Senses: abnormal vision, cataract, conjunctivitis, deafness, eye pain, taste perversion, tinnitus, vestibular disorder;

Urinary System: abnormal urine, hematuria, increased BUN, micturition urgency, nocturia, polyuria, pyelonephritis, urinary incontinence.

*NOS = Not Otherwise Specified.

Psoriasis: The principal adverse reactions associated with the use of cyclosporine in patients with psoriasis are renal dysfunction, headache, hypertension, hypertriglyceridemia, hirsutism/hypertrichosis, paresthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhea, abdominal discomfort, lethargy, and musculoskeletal or joint pain.

In psoriasis patients treated in U.S. controlled clinical studies within the recommended dose range, cyclosporine therapy was discontinued in 1.0% of the patients because of hypertension and in 5.4% of the patients because of increased creatinine. In the majority of cases, these changes were reversible after dose reduction or discontinuation of cyclosporine.

There has been one reported death associated with the use of cyclosporine in psoriasis. A 27 year old male developed renal deterioration and was continued on cyclosporine. He had progressive renal failure leading to death.

Frequency and severity of serum creatinine increases with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced and may result in irreversible renal damage without dose reduction or discontinuation.

Continued on next page

Gengraf—Cont.

[See table below]

The following events occurred in 1% to less than 3% of psoriasis patients treated with cyclosporine:

Body as a Whole: fever, flushes, hot flushes; ***Cardiovascular:*** chest pain; ***Central and Peripheral Nervous System:*** appetite increased, insomnia, dizziness, nervousness, vertigo; ***Gastrointestinal:*** abdominal distention, constipation, gingival bleeding; ***Liver and Biliary System:*** hyperbilirubinemia; ***Neoplasms:*** skin malignancies [squamous cell (0.9%) and basal cell (0.4%) carcinomas]; ***Reticuloendothelial:*** platelet, bleeding, and clotting disorders, red blood cell disorder; ***Respiratory:*** infection, viral and other infection; ***Skin and Appendages:*** acne, folliculitis, keratosis, pruritus, rash, dry skin; ***Urinary System:*** micturition frequency; ***Vision:*** abnormal vision.

Mild hypomagnesemia and hyperkalemia may occur but are asymptomatic. Increases in uric acid may occur and attacks of gout have been rarely reported. A minor and dose related hyperbilirubinemia has been observed in the absence of hepatocellular damage. Cyclosporine therapy may be associated with a modest increase of serum triglycerides or cholesterol. Elevations of triglycerides (>750 mg/dL) occur in about 15% of psoriasis patients; elevations of cholesterol (>300 mg/dL) are observed in less than 3% of psoriasis patients. Generally these laboratory abnormalities are reversible upon dose reduction or discontinuation of cyclosporine.

OVERDOSAGE

There is a minimal experience with cyclosporine overdosage. Forced emesis can be of value up to 2 hours after administration of Gengraf™ (cyclosporine capsules, USP [MODIFIED]). Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. General supportive measures and symptomatic treatment should be followed in all cases of overdosage. Cyclosporine is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral dosage at which half of experimental animals are estimated to die is 31 times, 39 times and >54 times the human maintenance dose for transplant patients (6 mg/kg; corrections based on body surface area) in mice, rats, and rabbits.

DOSAGE AND ADMINISTRATION

Gengraf™ (cyclosporine capsules, USP [MODIFIED]) has increased bioavailability in comparison to Sandimmune®* (cyclosporine [NON-MODIFIED]). Gengraf™ and Sandimmune®* (cyclosporine [NON-MODIFIED]) are not bioequivalent and cannot be used interchangeably without physician supervision.

The daily dose of Gengraf™ (cyclosporine capsules, USP [MODIFIED]) should always be given in two divided doses (BID). It is recommended that Gengraf™ be administered on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

Newly Transplanted Patients: The initial oral dose of Gengraf™ (cyclosporine capsules, USP [MODIFIED]) can be given 4–12 hours prior to transplantation or be given postoperatively. The initial dose of Gengraf™ varies depending on the transplanted organ and the other immunosuppressive agents included in the immunosuppressive protocol. In newly transplanted patients, the initial oral dose of Gengraf™ is the same as the initial oral dose of cyclosporine (NON-MODIFIED). Suggested initial doses are available from the results of a 1994 survey of the use of cyclosporine (NON-MODIFIED) in U.S. transplant centers. The mean ± SD initial doses were 9±3 mg/kg/day for renal transplant patients (75 centers), 8±4 mg/kg/day for liver transplant patients (30 centers), and 7±3 mg/kg/day for heart transplant patients (24 centers). Total daily doses were divided into two equal daily doses. The Gengraf™ dose is subsequently adjusted to achieve a pre-defined cyclosporine blood concentration (*see DOSAGE AND ADMINISTRATION, Blood Concentration Monitoring in Transplant Patients, below*). If cyclosporine trough blood concentrations are used, the target range is the same for Gengraf™ as for cyclosporine (NON-MODIFIED). Using the same trough concentration target range for Gengraf™ as for cyclosporine (NON-MODIFIED) results in greater cyclosporine exposure when Gengraf™ is administered (*see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption*). Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower Gengraf™ doses may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended initially. Different tapering dosage schedules of prednisone appear to achieve similar results. A representative dosage schedule based on the patient's weight started with 2.0 mg/kg/day for the first 4 days tapered to 1.0 mg/kg/day by 1 week, 0.6 mg/kg/day by 2 weeks, 0.3 mg/kg/day by 1 month, and 0.15 mg/kg/day by 2 months and thereafter as a maintenance dose. Steroid doses may be further tapered on an individualized basis depending on status of patient and function of graft. Adjustments in dosage of prednisone must be made according to the clinical situation.

Conversion from Sandimmune®* (cyclosporine [NON-MODIFIED]) to Gengraf™ (cyclosporine capsules, USP [MODIFIED]) in Transplant Patients: In transplanted patients who are considered for conversion to Gengraf™ from Sandimmune®* (cyclosporine [NON-MODIFIED]), Gengraf™ should be started with the same daily dose as was previously used with Sandimmune®* (cyclosporine [NON-MODIFIED]) (1:1 dose conversion). The Gengraf™ dose should subsequently be adjusted to attain the pre-conversion cyclosporine blood trough concentration. Using the same trough concentration target range for Gengraf™ as for Sandimmune®* (cyclosporine [NON-MODIFIED]) results in greater cyclosporine exposure when Gengraf™ is administered (*see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption*). Patients with suspected poor absorption of Sandimmune®* (cyclosporine [NON-MODIFIED]) require different dosing strategies (*see DOSAGE AND ADMINISTRATION, Transplant Patients with Poor Absorption of Sandimmune®* (cyclosporine [NON-MODIFIED]), below*). In some patients, the increase in blood trough concentration is more pronounced and may be of clinical significance.

Until the blood trough concentration attains the pre-conversion value, it is strongly recommended that the cyclosporine blood trough concentration be monitored every 4 to 7 days after conversion to Gengraf™. In addition, clinical safety parameters such as serum creatinine and blood pressure should be monitored every two weeks during the first two months after conversion. If the blood trough concentrations are outside the desired range and/or if the clinical safety parameters worsen, the dosage of Gengraf™ must be adjusted accordingly.

Transplant Patients with Poor Absorption of Sandimmune®* (cyclosporine [NON-MODIFIED]): Patients with lower than expected cyclosporine blood trough concentrations in relation to the oral dose of Sandimmune®* (cyclosporine [NON-MODIFIED]) may have poor or inconsistent absorption of cyclosporine from Sandimmune®* (cyclosporine [NON-MODIFIED]). After conversion to Gengraf™ (cyclosporine capsules, USP [MODIFIED]), patients tend to have higher cyclosporine concentrations. **Due to the increase in bioavailability of cyclosporine following conversion to Gengraf™, the cyclosporine blood trough concentration may exceed the target range. Particular caution should be exercised when converting patients to Gengraf™ at doses greater than 10 mg/kg/day.** The dose of Gengraf™ should be titrated individually based on cyclosporine trough concentrations, tolerability, and clinical response. In this population the cyclosporine blood trough concentration should be measured more frequently, at least twice a week (daily, if initial dose exceeds 10 mg/kg/day) until the concentration stabilizes within the desired range.

Rheumatoid Arthritis: The initial dose of Gengraf™ (cyclosporine capsules, USP [MODIFIED]) is 2.5 mg/kg/day, taken twice daily as a divided (BID) oral dose. Salicylates, nonsteroidal anti-inflammatory agents, and oral corticosteroids may be continued (*see WARNINGS and PRECAUTIONS: Drug Interactions*). Onset of action generally occurs between 4 and 8 weeks. If insufficient clinical benefit is seen and tolerability is good (including serum creatinine less than 30% above baseline), the dose may be increased by 0.5–0.75 mg/kg/day after 8 weeks and again after 12 weeks to a maximum of 4 mg/kg/day. If no benefit is seen by 16 weeks of therapy, Gengraf™ therapy should be discontinued.

Dose decreases by 25%-50% should be made at any time to control adverse events, e.g., hypertension elevations in serum creatinine (30% above patient's pretreatment level) or clinically significant laboratory abnormalities (*see WARNINGS and PRECAUTIONS*). If dose reduction is not effective in controlling abnormalities or if the adverse event or abnormality is severe, Gengraf™ should be discontinued. The same initial dose and dosage range should be used if Gengraf™ is combined with the recommended dose of methotrexate. Most patients can be treated with Gengraf™ doses of 3 mg/kg/day or below when combined with methotrexate doses of up to 15 mg/week (*see CLINICAL PHARMACOLOGY, Clinical Trials*).

There is limited long-term treatment data. Recurrence of rheumatoid arthritis disease activity is generally apparent within four weeks after stopping cyclosporine.

Psoriasis: The initial dose of Gengraf™ (cyclosporine capsules, USP [MODIFIED]) should be 2.5 mg/kg/day. Gengraf™ should be taken twice daily, as a divided (1.25 mg/kg BID) oral dose. Patients should be kept at that dose for at least 4 weeks, barring adverse events. If significant clinical improvement has not occurred in patients by that time, the patient's dosage should be increased at 2 week intervals. Based on patient response, dose increases of approximately 0.5 mg/kg/day should be made to a maximum of 4.0 mg/kg/day.

Dose decreases by 25%-50% should be made at any time to control adverse events, e.g., hypertension, elevations in serum creatinine (≥25% above the patient's pretreatment level), or clinically significant laboratory abnormalities. If dose reduction is not effective in controlling abnormalities, or if the adverse event or abnormality is severe, Gengraf™ should be discontinued (*see PRECAUTIONS, Special Monitoring of Psoriasis Patients*).

Patients generally show some improvement in the clinical manifestations of psoriasis in 2 weeks. Satisfactory control and stabilization of the disease may take 12–16 weeks to achieve. Results of a dose-titration clinical trial with Gengraf™ indicate that an improvement of psoriasis by 75% or more (based on PASI) was achieved in 51% of the patients after 8 weeks and in 79% of the patients after 12 weeks. Treatment should be discontinued if satisfactory response cannot be achieved after 6 weeks at 4 mg/kg/day or the patient's maximum tolerated dose. Once a patient is adequately controlled and appears stable the dose of Gengraf™ should be lowered, and the patient treated with the lowest dose that maintains an adequate response (this should not necessarily be total clearing of the patient). In clinical trials, cyclosporine doses at the lower end of the recommended dosage range were effective in maintaining a satisfactory response in 60% of the patients. Doses below 2.5 mg/kg/day may also be equally effective.

Upon stopping treatment with cyclosporine, relapse will occur in approximately six weeks (50% of the patients) to 16

Adverse Events Occurring in 3% or More of Psoriasis Patients in Controlled Clinical Trials

Body System*	Preferred Term	Cyclosporine (MODIFIED) (N=182)	Cyclosporine (NON-MODIFIED) (N=185)
Infection or Partial Infection		24.7%	24.3%
	Influenza-like Symptoms	9.9%	8.1%
	Upper Respiratory Tract Infections	7.7%	11.3%
Cardiovascular System		28.0%	25.4%
	Hypertension**	27.5%	25.4%
Urinary System		24.2%	16.2%
	Increased Creatinine	19.8%	15.7%
Central and Peripheral Nervous System		26.4%	20.5%
	Headache	15.9%	14.0%
	Paresthesia	7.1%	4.8%
Musculoskeletal System		13.2%	8.7%
	Arthralgia	6.0%	1.1%
Body As a Whole - General		29.1%	22.2%
	Pain	4.4%	3.2%
Metabolic and Nutritional		9.3%	9.7%
Reproductive, Female		8.5% (4 of 47 females)	11.5% (6 of 52 females)
Resistance Mechanism		18.7%	21.1%
Skin and Appendages		17.6%	15.1%
	Hypertrichosis	6.6%	5.4%
Respiratory System		5.0%	6.5%
	Bronchospasm, Coughing, Dyspnea, Rhinitis	5.0%	4.9%
Psychiatric		5.0%	3.8%
Gastrointestinal System		19.8%	28.7%
	Abdominal Pain	2.7%	6.0%
	Diarrhea	5.0%	5.9%
	Dyspepsia	2.2%	3.2%
	Gum Hyperplasia	3.8%	6.0%
	Nausea	5.5%	5.9%
White cell and RES		4.4%	2.7%

* Total percentage of events within the system.

** Newly occurring hypertension = SBP ≥160 mm Hg and/or DBP ≥90 mm Hg.

weeks (75% of the patients). In the majority of patients rebound does not occur after cessation of treatment with cyclosporine. Thirteen cases of transformation of chronic plaque psoriasis to more severe forms of psoriasis have been reported. There were 9 cases of pustular and 4 cases of erythrodermic psoriasis. Long term experience with Gengraf™ in psoriasis patients is limited and continuous treatment for extended periods greater than one year is not recommended. Alternation with other forms of treatment should be considered in the long term management of patients with this life long disease.

Blood Concentration Monitoring in Transplant Patients: Transplant centers have found blood concentration monitoring of cyclosporine to be an essential component of patient management. Of importance to blood concentration analysis are the type of assay used, the transplanted organ, and other immunosuppressant agents being administered. While no fixed relationship has been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustments, and the assessment of compliance.

Various assays have been used to measure blood concentrations of cyclosporine. Older studies using a non-specific assay often cited concentrations that were roughly twice those of the specific assays. Therefore, comparison between concentrations in the published literature and an individual patient concentration using current assays must be made with detailed knowledge of the assay methods employed. Current assay results are also not interchangeable and their use should be guided by their approved labeling. A discussion of the different assay methods is contained in *Annals of Clinical Biochemistry* 1994;31:420-446. While several assays and assay matrices are available, there is a consensus that parent-compound-specific assays correlate best with clinical events. Of these, HPLC is the standard reference, but the monoclonal antibody RIAs and the monoclonal antibody FPIA offer sensitivity, reproducibility, and convenience. Most clinicians base their monitoring on trough cyclosporine concentrations. *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring* (1992) contains a broad discussion of cyclosporine pharmacokinetics and drug monitoring techniques. Blood concentration monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED

Gengraf™ Capsules (cyclosporine capsules, USP [MODIFIED])

25 mg

Oval, white imprinted in blue, the corporate logo, 25 mg, and the Abbo-Code OR.

Packages of 30 unit-dose blisters. (NDC 0074-6463-32).

100 mg

Oval, white, with two blue stripes, imprinted in blue, the corporate logo, 100 mg, and Abbo-Code OT.

Packages of 30 unit-dose blisters. (NDC 0074-6479-32).

Store and Dispense: In the original unit-dose container at controlled room temperature 15°–30°C (59°–86°F). (See USP).

*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corporation.

TM-Trademark ©Abbott

Manufactured by: Abbott Laboratories North Chicago, IL 60064, U.S.A.

Distributed by: SangStat Medical Corporation Fremont, CA 94555, U.S.A.

Revised: January, 2000

Ref. 03-4999-R1

Shown in Product Identification Guide, page 303

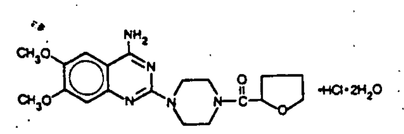
HYTRIN® ℞

(terazosin hydrochloride)
Capsules

DESCRIPTION

HYTRIN (terazosin hydrochloride), an alpha-1-selective adrenoceptor blocking agent, is a quinazoline derivative represented by the following chemical name and structural formula:

(RS)-Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]-, monohydrochloride, dihydrate.



Terazosin hydrochloride is a white, crystalline substance, freely soluble in water and isotonic saline and has a molecular weight of 459.93. HYTRIN capsules (terazosin hydrochloride capsules) for oral ingestion are supplied in four dosage strengths containing terazosin hydrochloride equivalent to 1 mg, 2 mg, 5 mg, or 10 mg of terazosin.

Inactive Ingredients:

1 mg capsules: gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

2 mg capsules: D&C yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

5 mg capsules: D&C red No. 28, FD&C red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

10 mg capsules: FD&C blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

A. Benign Prostatic Hyperplasia (BPH)

The symptoms associated with BPH are related to bladder outlet obstruction, which is comprised of two underlying components: a static component and a dynamic component. The static component is a consequence of an increase in prostate size. Over time, the prostate will continue to enlarge. However, clinical studies have demonstrated that the size of the prostate does not correlate with the severity of BPH symptoms or the degree of urinary obstruction. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck, leading to constriction of the bladder outlet. Smooth muscle tone is mediated by sympathetic nervous stimulation of alpha-1 adrenoceptors, which are abundant in the prostate, prostatic capsule and bladder neck. The reduction in symptoms and improvement in urine flow rates following administration of terazosin is related to relaxation of smooth muscle produced by blockade of alpha-1 adrenoceptors in the bladder neck and prostate. Because there are relatively few alpha-1 adrenoceptors in the bladder body, terazosin is able to reduce the bladder outlet obstruction without affecting bladder contractility.

Terazosin has been studied in 1222 men with symptomatic BPH. In three placebo-controlled studies, symptom evaluation and uroflowmetric measurements were performed approximately 24 hours following dosing. Symptoms were quantified using the Boyarsky Index. The questionnaire evaluated both obstructive (hesitancy, intermittency, terminal dribbling, impairment of size and force of stream, sensation of incomplete bladder emptying) and irritative (nocturia, daytime frequency, urgency, dysuria) symptoms by rating each of the 9 symptoms from 0–3, for a total score of 27 points. Results from these studies indicated that terazosin statistically significantly improved symptoms and peak urine flow rates over placebo as follows:

	Symptom Score (Range 0-27)			Peak Flow Rate (mL/sec)		
	N	Mean Baseline	Mean Change (%)	N	Mean Baseline	Mean Change (%)
Study 1 (10 mg)ᵃ						
Titration to fixed dose (12 wks)						
Placebo	55	9.7	−2.3 (24)	54	10.1	+1.0 (10)
Terazosin	54	10.1	−4.5 (45)*	52	8.8	+3.0 (34)*
Study 2 (2, 5, 10, 20 mg)ᵇ						
Titration to response (24 wks)						
Placebo	89	12.5	−3.8 (30)	88	8.8	+1.4 (16)
Terazosin	85	12.2	−5.3 (43)*	84	8.4	+2.9 (35)*
Study 3 (1, 2, 5, 10 mg)ᶜ						
Titration to response (24 wks)						
Placebo	74	10.4	−1.1 (11)	74	8.8	+1.2 (14)
Terazosin	73	10.9	−4.6 (42)*	73	8.6	+2.6 (30)*

ᵃ Highest dose 10 mg shown.
ᵇ 23% of patients on 10 mg, 41% of patients on 20 mg.
ᶜ 67% of patients on 10 mg.
* Significantly ($p \leq 0.05$) more improvement than placebo.

In all three studies, both symptom scores and peak urine flow rates showed statistically significant improvement from baseline in patients treated with terazosin from week 2 (or the first clinic visit) and throughout the study duration.

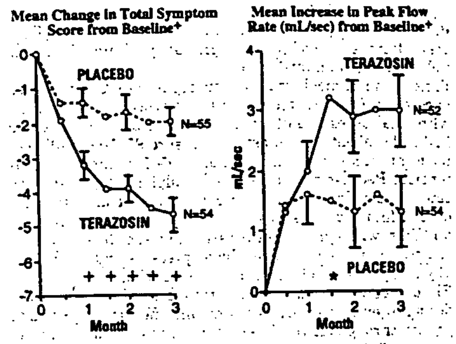
Analysis of the effect of terazosin on individual urinary symptoms demonstrated that compared to placebo, terazosin significantly improved the symptoms of hesitancy, intermittency, impairment in size and force of urinary stream, sensation of incomplete emptying, terminal dribbling, daytime frequency and nocturia.

Global assessments of overall urinary function and symptoms were also performed by investigators who were blinded to patient treatment assignment. In studies 1 and 3, patients treated with terazosin had a significantly ($p \leq 0.001$) greater overall improvement compared to placebo treated patients.

In a short term study (Study 1), patients were randomized to either 2, 5 or 10 mg of terazosin or placebo. Patients randomized to the 10 mg group achieved a statistically significant response in both symptoms and peak flow rate compared to placebo (Figure 1).

[See figure 1 at top of next column]

Figure 1
Study 1

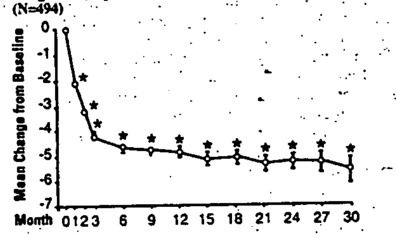


\+ for baseline values see above table
* $p \leq 0.05$, compared to placebo group

In a long-term, open-label, non-placebo controlled clinical trial, 181 men were followed for 2 years and 58 of these men were followed for 30 months. The effect of terazosin on urinary symptom scores and peak flow rates was maintained throughout the study duration (Figures 2 and 3):

Figure 2

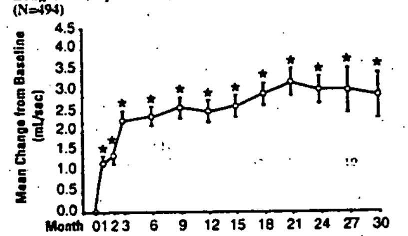
Mean Change in Total Symptom Score from Baseline Long-Term, Open-Label, Non-Placebo Controlled Study (N=494)



* $p \leq 0.05$ vs. baseline
mean baseline = 10.7

Figure 3

Mean Change in Peak Flow Rate from Baseline Long-Term, Open-Label, Non-Placebo Controlled Study (N=494)



* $p \leq 0.05$ vs. baseline
mean baseline = 9.9

In this long-term trial, both symptom scores and peak urinary flow rates showed statistically significant improvement suggesting a relaxation of smooth muscle cells.

Although blockade of alpha-1 adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, terazosin treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect:

Mean Changes in Blood Pressure from Baseline to Final Visit in all Double-Blind, Placebo-Controlled Studies

		Normotensive Patients DBP ≤90 mm Hg		Hypertensive Patients DBP >90 mm Hg	
	Group	N	Mean Change	N	Mean Change
SBP (mm Hg)	Placebo	293	−0.1	45	−5.8
	Terazosin	519	−3.3*	65	−14.4*
DBP (mm Hg)	Placebo	293	+0.4	45	−7.1
	Terazosin	519	−2.2*	65	−15.1*

* $p \leq 0.05$ vs. placebo

B. Hypertension

In animals, terazosin causes a decrease in blood pressure by decreasing total peripheral vascular resistance. The vasodilatory hypotensive action of terazosin appears to be pro-

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